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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/764,359	01/19/2001	Lola M. Reid	320727.50601	7133

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/764,359	REID ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-9,12-21 and 23-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-4, 6-9, 12-21 and 23-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 1/26/07 was entered.

Amended claims 1, 3-4, 6-9, 12-21 and 23-34 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, for New Matter was withdrawn in light of Applicant's amendment and arguments.

The provisional rejection under 35 U.S.C. 101 as claiming the same invention as that of copending Application No. 10/620433 was withdrawn upon review of the pending claims in the co-pending application.

The provisional rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/944,919 in view of Faris (U.S. 6,129,911 with the effective filing date of 7/10/1998; Cited previously) and Brasile (US 5,843,024) was withdrawn in light of Applicant's amendment to the pending claims in the co-pending application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-4, 6-9, 12-21 and 23-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reid et al. (WO 95/13697; IDS) in view of Faris (U.S. 6,129,911 with the effective filing date of 7/10/1998; Cited previously) and Brasile (US 5,843,024) for the same reasons already set forth in the Office Action mailed on 7/26/06 (pages 4-8). ***The same rejection is restated below.***

Reid et al. discloses methods for isolating hepatoblasts comprising liver stem cells (pluripotent precursors) and committed precursors for either hepatocytes and bile duct cells using panning technologies and multiparametric FAC sorting from a single cell suspension of liver cells (see Summary of Invention). Reid et al. states "The methods of the invention have been developed using embryonic and neonatal livers from rats, however, the method of the invention offers a systemic approach to isolating hepatoblasts from any age from any species" (page 4, lines 6-10). This statement includes the isolation of hepatoblasts from adult liver (see page 43). Reid et al. also notes that hepatoblasts that are found in a high proportion of liver cells in early

embryonic livers and in small number located periportally in adult livers (page 3, line 35 continues to line 1 of page 4). In the disclosed method (page 14, lines 9-15 for example), livers were dissected from donors, and placed into fresh ice-cold HBSS (should be about 4^0C). Reid et al. also teaches that the tendency of isolated cells to aggregate is prevented by maintaining the cells at 4^0C and by removing calcium with EGTA (page 39, lines 24-33). Panned cells in the methods taught by Reid et al are sorted for multiple markers that distinguish subcategories of hepatic precursor cell populations, with the identified markers include: (a) the extent of granularity as measured by side scatter on fluorescence activated cell sorting, (b) the extent of autofluorescence and (c) the expression of a hepatic cell marker (page 12, lines 23-34).

Reid et al does not specifically teach a method of processing a non-fetal donor liver tissue or procuring liver progenitor cells from a liver tissue or processing a liver tissue obtained between about 2 hours and about 30 hours postmortem or between about 2 hours and 30 hours.

At the effective filing date of the present application (1/19/00), Faris already taught methods for isolating liver cell clusters comprising a liver stem cell and a hepatocyte, and a population of isolated liver stem cells from adult liver tissues from various species such as a mouse, a pig or a human; and that the liver tissues can be obtained from mammalian organ donors including deceased donors or cadavers (these donors do not have heart-beats, see col. 5, lines 3-25 and Summary of Invention).

Additionally, Brasile also disclosed a process for inducing repair of ischemically damaged organs and tissues (e.g., liver, kidney, heart) to the degree that impairment of

function can be reversed and preventing further tissue damage during restoration of the circulation of the treated organ or tissue (see at least Summary of the Invention, col. 4, lines 29-32). In an exemplification, Brasile taught specifically a process used to overcome the effects of warm ischemia in liver deprived of blood flow, and support a repair process to the degree that impairment of liver function can be reversed, comprising the steps of flushing and perfusing for approximately 2 hours in the resustation of most livers deprived of blood flow for between about 0.5 to 4 hours for resumption of organ function (example 9, cols. 17-18).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings of Reid et al. by also obtaining liver tissues from deceased donors or cadavers, including human deceased donors and cadavers, for the preparation of hepatoblast cell populations and that these liver tissues should be obtained as fresh as possible to avoid cell death in the harvested tissues caused by warm ischemia that ensues rapidly upon death of an organism, including liver tissues deprived of blood flow for between about 0.5 to 4 hours and subjected to the treatment of flushing and perfusion for approaximately 2 hours, in light of the teachings of Faris and Brasile.

An ordinary skilled artisan would have been motivated to carry out the above modifications because liver tissues from deceased donors and cadavers, particularly from humans, are available for obtaining an enriched population of liver stem and/or progenitor cells, and that liver tissues of at least up to 6 hours postmortem that have

been subjected to the process taught by Brasile still retain organ function and without further tissue damage.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Reid et al, Farris, and Brasile, coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 1/26/07 (pages 7-11) have been fully considered but they are respectfully not found persuasive.

Applicants argue that no reference in the art teaches or suggests a method of processing a non-fetal donor liver tissue or procuring liver progenitor cells from a liver tissue obtained between about 2 hours and 30 hours postmortem. Neither Faris nor Brasile cure the deficiency for the Reid et al primary reference. For example, Faris nowhere teaches or suggests that liver progenitor cells can be isolated from liver tissue obtained about 2 hours and 30 hours postmortem, and the method for isolating progenitors actually disclosed by Faris is an isolation process that begins immediately following anesthetization of the donor. Brasile suggests that flushing and perfusion of livers with a "resuscitation solution" can be used to "overcome the effects of warm

ischemia in liver deprived of blood flow, and support a repair process to the degree that impairment of liver function can be reversed.", however Brasile provides no evidence of repair or function with example 9 is a prophetic example. Moreover, there is no teaching or suggestion that progenitors can be isolated from these "impairment-reversed" livers, let alone between about "2 hours and 30 hours postmortem". Applicants further argue that there is no motivation in the cited references that one of ordinary skilled would have had the motivation to isolate stem cells from any liver tissue obtained between about 2 hours and about 30 hours postmortem, including resuscitated ones. Lastly, Applicants argue that there is no reasonable expectation of success. Particularly, Applicants rely on the paragraph "while methods of isolating liver precursor cells are known in the art, until the reduction to the practice of the present invention it was not known that progenitor cells can be isolated from what was considered in the prior art as a "useless" organ". Applicants also noted that the term "useless organ" is used in the context for transplantation. Additionally, Applicants argue that the isolation of progenitor cells from livers deemed useless was completely unexpected since all known prior art references regarded ischemically damaged organs as being totally useless for any meaningful purpose because the scientific community assumed that the liver autolyzes within less than an hour, and that progenitor cells- - being particularly sensitive to ischemic damage—would be the first cells to die.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For the instant case, Reid et al. discloses clearly methods for isolating hepatoblasts comprising liver stem cells (pluripotent precursors) and committed precursors from liver tissues derived any age from any species, including from adult liver; while Faris teaches methods for isolating liver cell clusters comprising a liver stem cell and a hepatocyte, and a population of isolated liver stem cells from adult liver tissues from various species such as a mouse, a pig or a human; and that the liver tissues can be obtained from mammalian organ donors including deceased donors or cadavers. Additionally, Brasile already disclosed a process for inducing repair of ischemically damaged organs and tissues (e.g., liver, kidney, heart) to the degree that impairment of function can be reversed and preventing further tissue damage during restoration of the circulation of the treated organ or tissue, including liver tissues deprived of blood flow for between about 0.5 to 4 hours and subjected to the treatment of flushing and perfusion for approaximately 2 hours. As already stated above, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings of Reid et al. by also obtaining liver tissues from deceased donors or cadavers, including human deceased donors and cadavers, for the preparation of hepatoblast cell populations and that these liver tissues should be obtained as fresh as possible to avoid cell death in the harvested tissues caused by warm ischemia that ensues rapidly upon death of an organism, including liver tissues deprived of blood flow for between about 0.5 to 4 hours and subjected to the treatment of flushing and perfusion for approaximately 2 hours, in light of the teachings of Faris and Brasile.

Please note that the teachings of Faris are not limited only to the disclosed example. Faris teaches clearly the use of liver tissues obtained from mammalian organ donors including deceased donors or cadavers to the isolation of liver stem/progenitors. With respect to Applicant's doubts on the enablement of Brasile's teachings, please refer to claims issued to Brasile. Issued claims of a US patent are considered to be valid until proven otherwise.

An ordinary skilled artisan would have been motivated to carry out the modifications set forth above because liver tissues from deceased donors and cadavers, particularly from humans, are available for obtaining an enriched population of liver stem and/or progenitor cells, and that liver tissues of at least up to 6 hours postmortem that have been subjected to the process taught by Brasile still retain organ function and without further tissue damage. Even though Faris clearly teaches that liver tissues can be obtained from deceased donors and even from cadavers (many hours or days after deaths) for the isolation of liver stem/progenitor cells, it is still desirable that liver tissues should be obtained as fresh as possible to avoid cell death in the harvested tissues caused by warm ischemia that ensues rapidly upon death of an organism, including liver tissues deprived of blood flow for between about 0.5 to 4 hours and subjected to the treatment of flushing and perfusion for approaximately 2 hours as taught by Brasile. Please note that this concept is derived from the totality of the combined teachings of Reid et al., Faris and Brasile, and not from the examiner's personal opinions.

With respect to the issue of no reasonable expectation of success, once again please note that Faris clearly teaches that liver tissues can be obtained from deceased donors and even from cadavers (many hours or days after deaths) for the isolation of liver stem/progenitor cells, let alone for tissues obtained from a donor between about 2 hours and 30 hours post-mortem. With respect to the cited paragraph, the term "useless organ" is used only in the context for transplantation into a patient, and not as a tissue or liver source for the isolation of liver stem/progenitor cells. There is no factual evidence of record indicating or even suggesting that stem/progenitor cells no longer exist in any tissues harvested later than 30 hours postmortem, let alone between about 2 hours and 30 hours postmortem, and particularly in light of the teachings of Faris discussed above.

Accordingly, claims 1, 3-4, 6-9, 12-21 and 23-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reid et al. (in view of Faris and Brasile for the same reasons already set forth in the Office Action mailed on 7/26/06 (pages 4-8).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2-4, 8-9, 12-21, 23-34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,069,005 or claims 1-32 of US Patent No. 6,242,252 in view of Faris (U.S. 6,129,911 with the effective filing date of 7/10/1998; Cited previously) and Brasile (US 5,843,024) for the same reasons already set forth in Office action mailed on 7/26/06 (pages 9-12). ***The same rejection is restated below.***

The instant claims are directed to a method of processing non-fetal donor liver tissue to obtain an enriched population of progenitor cells, a method of procuring liver progenitor cells, a method of processing a liver tissue having at least one progenitor cell population or at least one diploid cell population, said methods comprise the step of providing non-fetal donor tissue obtained between about 2 hours and about 30 hours postmortem or harvesting a tissue from a donor having a non-beating heart between about 2 hours and 30 hours postmortem .

Claims 1-4 of U.S. Patent No. 6,069,005 are directed to a method of isolating hepatic progenitors from adult liver comprising the steps recited in claim 1.

Claims 1-32 of U.S. Patent No. 6,242,252 are drawn to a method of isolating hepatic progenitors from liver comprising the steps recited in either claim 1 or claim 14.

The claims of the present application differ from the claims of the U.S. Patent No. 6,069,005 or the claims of the U.S. Patent No. 6,242,252 in reciting specifically the step of providing non-fetal donor tissue obtained between about 2 hours and about 30 hours postmortem or harvesting a tissue from a donor having a non-beating heart between about 2 hours and 30 hours postmortem.

At the effective filing date of the present application (1/19/00), Faris already taught methods for isolating liver cell clusters comprising a liver stem cell and a hepatocyte, and a population of isolated liver stem cells from adult liver tissues from various species such as a mouse, a pig or a human; and that the liver tissues can be obtained from mammalian organ donors including deceased donors or cadavers (these donors do not have heart-beats, see col. 5, lines 3-25 and Summary of Invention).

Additionally, Brasile also disclosed a process for inducing repair of ischemically damaged organs and tissues (e.g., liver, kidney, heart) to the degree that impairment of function can be reversed and preventing further tissue damage during restoration of the circulation of the treated organ or tissue (see at least Summary of the Invention, col. 4, lines 29-32). In an exemplification, Brasile taught specifically a process used to overcome the effects of warm ischemia in liver deprived of blood flow, and support a repair process to the degree that impairment of liver function can be reversed, comprising the steps of flushing and perfusing for approximately 2 hours in the

resustation of most livers deprived of blood flow for between about 0.5 to 4 hours for resumption of organ function (example 9, cols. 17-18).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify claims 1-4 of U.S. Patent No. 6,069,005 or claims 1-32 of U.S. Patent No. 6,242,252 by also obtaining liver tissues from deceased donors or cadavers, including human deceased donors and cadavers, for the isolation of hepatic progenitors and that these liver tissues should be obtained as fresh as possible to avoid cell death in the harvested tissues caused by warm ischemia that ensues rapidly upon death of an organism, including liver tissues deprived of blood flow for between about 0.5 to 4 hours and subjected to the treatment of flushing and perfusion for approaximately 2 hours, in light of the teachings of Faris and Brasile.

An ordinary skilled artisan would have been motivated to carry out the above modifications because liver tissues from deceased donors and cadavers, particularly from humans, are available for obtaining an enriched population of liver stem and/or progenitor cells, and that liver tissues of at least up to 6 hours postmortem that have been subjected to the process taught by Brasile still retain organ function and without further tissue damage.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of either U.S. Patent No. 6,069,005 or U.S. Patent No. 6,242,252 with Farris, and Brasile, coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 1/26/07 (page 12) have been fully considered but they are respectfully not found persuasive.

Applicants presented the same arguments for those for the above rejection under 35 USC 103.

Please refer to the same Examiner's responses to Applicant's arguments for the above rejection under 35 USC 103.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D
PRIMARY EXAMINER